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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/579,383	05/26/2000	Joseph M. Vinetz	026.00101	7685

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EXAMINER
BASKAR, PADMAVATHI

ART UNIT	PAPER NUMBER
1645	10

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/579,383	VINETZ, JOSEPH M.	
	Examiner	Art Unit	
	Padmavathi v Baskar	1645	

-- The MAILING DATE of this communication appears on th cov r sh t with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) *13-22, 25-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12, 23, 24 and 46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-46* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Response to Amendment

1. The amendment filed on 11/25/02 has been entered into the record. Claims 1, 4, 5, 23 and 24 have been amended. New claim 46 has been added. Claims 1-12, 23, 24 and newly added claim 46 are under examination as an elected invention, said election made in Paper # 6

2. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

Rejections Withdrawn

3. In view of amendment to the claims, the examiner has withdrawn under 35 U.S.C. 112, second paragraph rejection for claims 1-12, 23 and 24.

Rejections Maintained

4. The rejection of claims 1-2 and 24 under 35 U.S.C. 102(b) as being anticipated by Sim et al 1989(Molecular and Biochemical Parasitology: 34:127-134) is maintained as set forth in the previous office action.

Claims are drawn to an isolated nucleic acid molecule encoding a Plasmodium falciparum chitinase; said nucleic acid is DNA and a DNA oligomer, which hybridizes to the nucleic acid molecule of claim 1.

With regard to an isolated nucleic acid molecule encoding a Plasmodium falciparum chitinase, the prior art discloses the nucleic acid molecule encoding chitinase from sporozoites of P. falciparum and P.berghei as the DNA obtained from infected mosquitoes encoding chitinase (page 129, right column, lines 1-5). The DNA was denatured and isolated on to the filters (see page 128, left column, first paragraph). Therefore, it meets the limitations of claims 1-2. DNA oligomer probes namely pPb3, p24B1-1 were hybridized to the nucleic acid (see figure 3 and figure 4) and thus read on claim 24. The prior art anticipated the claimed invention.

Applicants arguments filed on 11/25/02 have been fully considered but they are not deemed to be persuasive.

Applicant asserts that Sim et al does not disclose an isolated nucleic acid molecule as defined by the present specification on page14, lines 26-30, " isolated" refers to nucleic acid which has been separated from an organism in a substantially purified form.

It is the position of the office that the claims are read in light of the Specification. However, the breadth of the claims is broad (see MPEP 2173.04) and read on the cited prior art. Sim et al disclose that infected mosquitoes were crushed and the DNA from sporozoites was denatured and isolated on to the filters and thus meet the limitation "an isolated nucleic acid molecule" of the claimed invention. i. e., substantially purified form and separated from mosquitoes. Radiolabelled P.falciparum probe was shown to be (figure 3, rows a and b) hybridized with the isolated DNA on the filter and thus read on claim 24. Therefore, this rejection is maintained.

5. The rejection of claims 1-3, 6-12, and 24 under 35 U.S.C. 102(a) as being anticipated by Vinetz et al 1999(PNAS: 96:14061-14066) is maintained as set forth in the previous office action (Please note that the present rejection is under 35U.S.C. 102 (a) not under 102 (b) as stated in Paper # 7 of the previous Office action as the examiner is now aware that the article was published in November 1999).

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims are drawn to an isolated nucleic acid molecule encoding Plasmodium falciparum chitinase, wherein said DNA is cDNA, RNA, mRNA and a DNA oligomer, which hybridizes to the nucleic acid molecule of claim 1. Claims are also drawn to oligonucleotide complementary to at least a portion of the mRNA, expression vector and host cells.

Vinetz et al 1999 disclose an isolated nucleic acid molecule encoding P.falciparum chitinase, wherein said DNA (see abstract) is cDNA, RNA (see page 14062, right column, first paragraph), mRNA (see Figure 2c and Results: characterization of full length Chitinase gene) and a DNA oligomer capable of hybridizing to the nucleic acid (Figure 2). Plasmid pET32b, which expresses PfCHT1, is complementary to mRNA of the nucleic acid that encodes chitinase and is tranfected into E.coli host cells (see page 14064, left column). Thus, the prior art anticipated the claimed invention with respect to an isolated nucleic acid molecule encoding a P.falciparum chitinase.

Applicants arguments filed on 11/25/02 have been fully considered but they are not deemed to be persuasive.

Applicant asserts that Vinetz et al reference was published 11/23/1999 and the Office action in paper # 7 indicated that priority is granted as of 5/28/1999. Therefore, the rejection is improper and should be withdrawn.

It is the position of the office that the Office action, paper # 7 (paragraph # 2) has clearly indicated that claims 4 and 5 with respect to the SEQ.ID.NO: 1 and 3 accorded priority as of 5/28/99. However, the Office has not rejected the claims 4 and 5 under 35 U.S.C. 102(a) as being anticipated by Vinetz et al. The rejected claims are 1-3, 6-12, and 24 which are not drawn to SEQ.ID.NO: 1 and 3 and are drawn broadly to an isolated nucleic acid molecule encoding a Plasmodium falciparum chitinase, wherein said DNA is cDNA, RNA, mRNA and a DNA oligomer which hybridizes to the nucleic acid molecule of claim 1. Therefore, the rejection is properly applied to these claims as these claims are accorded priority as of the filing date of the present application (5/26/00).

6. The rejection of claims 1-12, 23, 24 and newly added claim 46 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, written Description Rejection and

the enablement rejection is maintained as set forth in the previous office action.

Claims are drawn to an isolated nucleic acid molecule encoding a P.falciparum chitinase, oligonucleotide complementary to portion of mRNA, expression vectors and host cells comprising the expression vectors. However, the specification discloses only SEQ.ID.NO: 1 that encodes a polypeptide disclosed in SEQ.ID.NO: 3 with regard to recombinant P.falciparum chitinase (see pages 72-73) expression vector, pET32b tranfected into DH10B E.coli host cells. In analyzing whether the written description requirement is met for genus claims (P.falciparum chitinase genes), it is first determined whether a representative number of species have been described by their complete structure. In the instant case, SEQ.ID.NO: 1 is the only chitinase among P.falciparum chitinases whose complete structure is disclosed.

Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence). In the instant case, the other identifying characteristics are the functional motifs such as secretory signal peptide sequence, substrate binding and catalytic sites of chitinase. Therefore, this limited information disclosed in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of cDNAs from all other Plasmodium falciparum chitinases besides SEQ.ID.NO: 1 at the time the application was filed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the Chitinase genes and because the genes are highly variant, the disclosure of specific nucleotide sequences and the ability to screen is insufficient to describe all genes of chitinase. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable all the genes of Plasmodium falciparum as broadly claimed. Thus it is concluded that the written description requirement is not satisfied for an isolated nucleic acid molecule encoding P.falciparum chitinase. Therefore, this limited information disclosed in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of cDNA besides SEQ.ID NO: 1 at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for all P.falciparum chitinase genes.

7. Since there is no written description support for multiple chitinase genes of Plasmodium falciparum, claims 1-12, 23 24 and newly added claim 46 are also rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid encoding P.falciparum sporozoites chitinase (SEQ.ID.NO: 1 and expression vector) does not reasonably provide enablement for any and all isolated nucleic acids encoding any and all Plasmodium falciparum chitinases (multiple genes encode multiple chitinase isoforms from ookinette, and gametocytes) as recited broadly in instant claims.

8. The rejection of claims 23 and newly added claim 46 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid molecule encoding a P.falciparum sporozoite said nucleotide molecule encoding an amino acid sequence as set forth in the SEQ.ID.NO: 3 does not reasonably provide enablement for an isolated polynucleotide encoding P.falciparum chitinase polypeptide, said polynucleotide encoding a first amino acid sequence having at least 90% amino acid identity to SEQ.ID.NO: 3 or an isolated nucleic acid molecule encoding a P.falciparum chitinase said nucleotide molecule as shown in SEQ.ID.NO: 1 with conservative substitutions is maintained as set forth in the previous Office action.

Scope of enablement requires that the specification teach those in the art to make and use the invention commensurate with the scope of the claim without undue experimentation include (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

With regard to %identity, the specification is not enabled for polypeptides which have an amino acid 90% sequence identity with SEQ.ID.NO 3 because it is unclear to one skilled in the art what sequences are embraced by the claim. If it is unclear to one skilled in the art what sequences are embraced by a claim which is based on a specification to determine percent identity, the specification is non-enabling, since one skilled in the art would not be able to make and use those sequences without undue experimentation. The specification is totally silent with regard to conservative substitutions in a nucleic acid molecule, SEQ.ID.NO: 1.

The specification provides guidance and direction with regard to an isolated polynucleotide encoding a polypeptide SEQ.ID.NO 3 which is designated as P.falciparum chitinase protein on page 26. However, there is no guidance or directions on how to make and use an isolated polynucleotide encoding a polypeptide, which has an amino acid 90% identity with SEQ.ID.NO 3 or an isolated nucleic acid molecule encoding a P.falciparum chitinase said nucleotide molecule as shown in SEQ.ID.NO: 1 with conservative substitutions.

It is well known that for proteins, for example, even a single amino acid change can destroy the function of the biomolecule. The effects of these changes are largely unpredictable as to which ones have a significant effect versus not. Further, specification is silent on how to make a protein with 90% sequence identity to SEQ.ID.NO: 3 or an isolated nucleic acid molecule encoding a P.falciparum chitinase said nucleotide molecule as shown in SEQ.ID.NO: 1 with conservative substitutions. Applicant failed to give direction to what modification have been done to SEQ.ID.NO 3 to give rise to 90% sequence identity to said polypeptide and what are the conservative substitutions in a nucleic acid molecule SEQ.ID.NO: 1 have been made. What changes would have an adverse effect on the function of this peptide is not predictable. It

is known in the art that proteins, which are obtained by substitutions, deletions, or modifications of the amino acids of a protein (in this case protein with 90% identity to SEQ.ID.NO: 3 is considered as a variant), alter the function of the protein. The amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still retain similar activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expected intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, the problem of predicting protein structure from mere sequence data of a single protein and in tum utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex (Bowie et al. Science, Vol. 247: 1990; p. 1306; p. 1308) is well outside the realm of routine experimentation.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed polypeptide in a manner reasonably correlated with the scope of the claims broadly including any number of insertions, deletions or substitutions that would encompass a biologically active variant of a Plasmodium chitinase as presently claimed. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made in the protein renders activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Applicants arguments filed on 11/25/02 have been fully considered but they are not deemed to be persuasive.

Applicant asserts that the amendment to the claim 1 would obviate the rejections. However, it is the position of the Office that claim 1 is claiming all chitinases in P.falciparum while the specification supports to only "an isolated nucleic acid molecule as set forth in SEQ.ID.NO: 1 encoding Plasmodium falciparum chitinase. Therefore, the rejections are maintained.

With regard to the rejection of claim 23, Applicant states that the present application as filed, indicates to one of ordinary skill in the art sufficient guidance and direction to make and use an isolated nucleic acid molecule encoding Plasmodium falciparum chitinase, said nucleic acid molecule encoding a first amino acid sequence having at least 90% amino acid identity to SEQ.ID.NO: 3 because the methods such as mutagenesis and screening are known which does not require undue experiments.

It is the position of the Office that while general techniques are known, the specification fails to teach what are the critical nucleic acid t can be modified and still achieve a nucleic acid molecule encoding a protein having at least 90% amino acid identity to SEQ.ID.NO: 3 with similar functional activity (i.e., chitinase activity in blocking malaria parasite transmission to mosquitoes). Further, the art teaches that proteins with replacement of single amino acid residues may lead to both structural and functional changes that would not retain the biological activity. Therefore, one skilled in the art would have reason to doubt the validity and functionality of the function an isolated nucleic acid molecule encoding Plasmodium falciparum chitinase, said nucleic acid molecule encoding a first amino acid sequence having at least 90% amino acid identity to SEQ.ID.NO: 3. Further, the specification does not disclose what other DNA from different stages of parasite, P.falciparum that encodes what other chitinases as the limitation "at least " broadly reads on any chitinase. Therefore, the rejections are maintained.

New Rejections Based on Amendment

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claim 46 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim 46 is rejected as being vague for the recitation of "conservative substitutions". It is not clear and difficult to understand what are the metes and bounds of conservative substitutions in a nucleic acid molecule as written.

11. Claim 24 is rejected under 35 U.S.C. 102(b) as being clearly anticipated by Boehringer Mannheim Biochemicals (1991 Catalog page 557), Stratagene (1991 Product Catalog, page

66), Gibco BRL (Catalogue & Reference Guide 1992, page 292), Promega (1993/1994 Catalog, pages 90-91) or New England BioLabs (Catalog 1986/1987, pages 60- -62).

The claim is drawn to a DNA oligomer, which hybridizes to the nucleic acid molecule of claim 1.

Boehringer Mannheim Biochemicals (1991 Catalog page 557), Stratagene (1991 Product Catalog, page 66), teach kits containing isolated packaged random 6-mer primers and random 9-mer primers. The random primer kits contain all possible 6 mer and 9 mer sequences for priming DNA sequences for labeling.

Gibco BRL (Catalogue & Reference Guide 1992, page 292), Promega (1993/1994 Catalog, pages 90-91) or New England BioLabs (Catalog 1986/1987, pages 60-62) each teach a wide variety of probes, primers and linkers of over 10 nucleotides in length.

As such, the random primers, probes and linkers anticipate the instant claim. The primers and linkers have been applied as relevant to the restriction map provided for an isolated nucleic acid molecule encoding a Plasmodium falciparum chitinase.

12. Information Disclosure Statement filed on 11/25/02(Paper # 10) is acknowledged and a signed copy is attached to this Office action.

Status of Claims

13. No claims are allowed.

Conclusion

14. This application contains claims 13-22, 25-45 drawn to an invention nonelected with traverse in Paper No. 6. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this

Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP ' 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Padma Baskar whose telephone number is (703) 308-8886. The examiner can normally be reached on Monday through Friday from 6:30 AM to 4 PM EST

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Padma Baskar Ph.D.

2/13/03

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